IN THE SPECIFICATION

Please insert the required "Brief Description of the Drawings" section shown below after line 3 on page 4 of the specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the N-terminal sequences of wild type hPRL and hGH and of the deletion mutants of hPRL are shown on Figure 1. Legend of Figure 1: Top: PRL (SEQ ID NO: 1) and GH (SEQ ID NO: 2) N-terminal sequences are aligned; the N-terminus is 9 residues longer in PRL, including a disulfide bond between Cys_4 and Cys_{11}. An arrow identifies putative helix 1 as predicted by homology modeling. Bottom: incremental deletions of hPRL N-terminus. Deletion of the 9 first residues (Δ1-9-hPRL) mimics N-terminus of hGH, whereas deletion of the 14 first residues (Δ1-14-hPRL) removes the N-terminus tail in its entirety.

Figure 2A and 2B depict the binding affinities of N-terminal and G129R-containing hPRL analogs. Fig. 2A shows the binding affinity of hPRL analogs was calculated as the ratio of their IC_{50} with respect to that of WT hPRL calculated from competition curves (regression in the linear part of sigmoids). Results presented in Figure 2A are representative of at least three independent experiments performed in duplicate. Fig. 2B shows a binding assay of the G129R-containing mutants.Representative competition curves obtained with the three analogs containing the Gly129→Arg mutation are shown in Figure 2B: WT hPRL (—●—); single mutant G129R-hPRL (—◆—); double mutant Δ1-9-G129R-hPRL (—■—); double mutant Δ1-14-G129R-hPRL (—▲—). The three curves are displaced to the right by ~1 order of magnitude compared to WT hPRL, reflecting 10 fold lower affinity for the receptor. Averaged from three independent experiments, IC_{50} were 166 ± 47 ng/ml for Δ1-9-G129R and 187 ± 49 ng/ml for Δ1-14-G129R, compared to 18 ± 5 ng/ml (for WT hPRL). None of the N-terminal deletion improves affinity compared to G129R-hPRL (single mutant).

Figure 3 shows agonism of N-terminal deleted analogs using the Nb2 cell proliferation assay. Figure 3A shows cell proliferation in presence of increasing concentrations of hPRL (—●—), Δ1-9-hPRL (—□—) and Δ1-14-hPRL (—△—); Figure 3B shows cell

proliferation in presence of increasing concentrations of hPRL (—●—), Δ1-10-hPRL (--∗--), Δ1-11-hPRL (--○--), Δ1-12-hPRL (--□--), Δ1-13-hPRL (--◇--).

Figure 4 shows the different mitogenic activities of analogs by the Ba/F3-hPRLR cell proliferation bioassay. Figure 4A shows proliferation of Ba/F3 cells in presence of increasing concentrations of hPRL (—●—), Δ1-9-hPRL (—□—) and Δ1-14-hPRL (—△—); Figure 4B shows proliferation of Ba/F3 cells in presence of increasing concentrations of hPRL (—●—), Δ1-10-hPRL (--∗--), Δ1-11-hPRL (--○--),Δ1-12-hPRL (--□--), Δ1-13-hPRL (--◇--).

Figure 5 provides data of one typical experiment performed in duplicate and representative of three experiments which depicts hPRL transcriptional activity (% of activity *vs.* WT hPRL maximal effect referred as 100%) in presence of increasing concentrations (μg/ml) of: hPRL (—●—), Δ1-9-hPRL (—□—),Δ1-14-hPRL (—△—), Δ1-10-hPRL (--∗--), Δ1-11-hPRL (--○--),Δ1-12-hPRL (--□--), Δ1-13-hPRL (--◇--).

Figure 6 shows agonism of G129R and double mutants by means of the Nb2 cell proliferation assay: cell proliferation without hPRL (□) and in presence of increasing concentrations of purified WT hPRL (■), G129R-hPRL (▩), Δ1-9-G129R-hPRL (☰) and Δ1-14-G129R-hPRL (▨).

Figures 7A and 7B shown agonism and antagonism. 7A shows agonism by activation of the LHRE-luciferase reporter gene by increasing concentrations of WT hPRL (■), and the three G129R-containing analogs, G129R-hPRL G129R-hPRL (▩), Δ1-9-G129R-hPRL (☰), and Δ1-14-G129R-hPRL (▨). The agonistic activity of G129R-hPRL is extremely reduced in this assay, reaching a maximal level <2% of hPRL activity. Similarly, none of the double mutant induced detectable level of luciferase activity, even when tested at extremely high concentrations (up to 50 μg/ml). The results demonstrating antagonism are shown in Figure 7B: Δ1-14-G129R-hPRL(—■—), Δ1-9-G129R-hPRL (—▲—), G129R-hPRL (—◆—).

Figures 8A and 8B show agonism and antagonism using the Ba/F3-hPRLR cell proliferation bioassay. Figure 8A shows agonism by cell proliferation in presence of increasing

concentrations of purified WT hPRL (■), G129R-hPRL (▓), Δ1-9-G129R-hPRL (≡), and Δ1-14-G129R-hPRL (▨). Maximal effect of WT hPRL is obtained at 10 ng/ml. G129R-hPRL induced sub-maximal proliferation with a dose-response curve displaced by 2 logs to the high concentrations. In contrast, none of the double mutants (Δ1-9-G129R-hPRL and Δ1-14-G129R-hPRL) induced significant proliferation. As in the Nb2 assay, the curve obtained for G129R-hPRL was displaced to the right by ~2 log units and achieved sub-maximal (50-80%) level compared to hPRL. At high concentrations, hPRL and G129R-hPRL displayed bell-shaped curves, a typical observation when using these ligands (KINET *et al.*, Recent Res. Devel. Endocrinol., 2, 1-24, 2001). Both Δ1-9-G129R-hPRL and Δ1-14-G129R-hPRL failed to display any agonistic activity, even at concentration as high as 10 μg/ml. Antagonistic assays were performed by competing a fixed concentration of WT hPRL (10 ng/ml) with increasing concentrations of the analogs. Figure 8B shows cell proliferation in presence of increasing concentrations of Δ1-9-G129R-hPRL (—■—), Δ1-14-G129R-hPRL (—▲—), G129R-hPRL (—◆—) competing with the fixed concentration of WT hPRL.

Figure 9 depicts blots describing kinase activation describe by Example 4. **A:** anti-MAPK blots: top panel (MAPK-P): phosphorylated MAPK; bottom panel: total MAPK (MAPK). **B:** densitometric quantification of MAPK-P blots (top panels).

Figure 10 shows Δ1-9G129R inhibition of PRL-induced Stat 3 and Stat 5 activation as shown by Example 5. **A:** anti-STAT blots: Top panel (P-Stat5 and P-Stat3): phosphorylated Stat5 and phosphorylated Stat3; Bottom panel (Stat5 and Stat3): total Stat5 and Stat3. **B:** densitometric quantification of anti-phosphorylated STAT blot (top panels).

Figure 11 shows that Δ1-9-G129R inhibits PRL-induced MAPK Constitutive activation as described in Example 6. **A:** anti-MAPK blots: Top panel (MAPK-P): phosphorylated MAPK; Bottom panel (MAPK): total MAPK. **B:** densitometric quantification of MAPK-P blots (top panels).

Figure 12 refers to antagonist (Δ1-9G129R-hPRL) as also described in Example 6. **A:** anti-MAPK blots: Top panel (MAPK-P): phosphorylated MAPK in the prostate ventral and dorsolateral lobes and in the presence (+) or absence (-) of Δ1-9G129R-hPRL mutant;

Bottom panel (MAPK): total MAPK in the same samples. **B:** densitometric quantification of anti-phosphorylated MAPK blot (top panels).